Recent Advances in Lung Cancer

Summary of Presentations from the 47th Annual Meeting of the American Society of Clinical Oncology (ASCO) 2011

Janakiraman Subramanian, MD,† Saiama N. Waqar, MD,*† Daniel Morgensztern, MD,‡ and Ramaswamy Govindan, MD*†*

Abstract: In the last several years, we have made slow but steady progress in developing new treatment strategies for patients with lung cancer. The use of molecularly targeted therapy has made a significant impact on the outcomes of patients with lung cancer. Further research is ongoing to identify more effective ways to target lung cancer. In the recently concluded 47th annual meeting of the American Society of Clinical Oncology, there were several presentations on novel targeted therapies for lung cancer, in addition to the effective and optimal use of existing cytotoxic and targeted therapies for lung cancer. For this review, we have selected presentations that primarily have an impact on clinical practice, and some presentations regarding emerging therapeutic agents.

Key Words: Lung cancer, NSCLC, Elderly patients, Maintenance chemotherapy, MetMAb, EML4-ALK, Pemetrexed, Erlotinib, Gefitinib, EGFR-TK mutation.

(*J Thorac Oncol.* 2012;7: 260–265)

The advent of molecularly targeted therapy represents a major advance in the treatment of lung cancer, with some remarkable success stories, including the development of tyrosine kinase (TK) inhibitors that successfully target the epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) inhibitors.[1,2] However, we are still far from realizing truly personalized therapy for patients with lung cancer. Targeted drugs have a meaningful therapeutic impact only in a small proportion of patients with lung cancer. For most of patients with advanced lung cancer, there are no well-established or effective targets and still rely on cytotoxic chemotherapy treatments. Furthermore, tumors that are initially sensitive to targeted therapy eventually develop resistance. There is a need for identifying new molecular targets for lung cancer, developing effective inhibitors for known and validated targets, such as K-RAS, and identifying methods to surmount the eventual development of resistance. Nevertheless, progress has been slow with only a handful of targeted therapies showing significant treatment benefit against lung cancer.

In the recently concluded 47th annual meeting of the American Society of Clinical Oncology (ASCO), there were several presentations on novel targeted therapies for lung cancer, in addition to the effective and optimal use of existing cytotoxic and targeted therapies for lung cancer. For this review, we have selected presentations that primarily have an impact on clinical practice, and some presentations on promising new findings regarding emerging therapeutic agents.

Metastatic Non-small Cell Lung Cancer

Personalized Therapy for Advanced Non-small Cell Lung Cancer

The Lung Cancer Mutation Consortium (LCMC) was established with the goal of developing personalized therapy for patients with advanced adenocarcinoma of the lung by studying tumor tissues.[3] The consortium consisted of 14 academic institutions and enrolled more than 1000 patients whose tumor specimens were tested for panel of molecular alterations, including mutations in the KRAS, EGFR, HER2, PIK3CA, AKT1, NRAS, MEK1 genes, and EML4-ALK fusion gene as well as MET amplification. Patients with activating EGFR-TK mutations were treated with erlotinib and patients with other driver mutations were offered participation in a clinical trial with an agent specific to the target, when possible.

Of the over 1000 patients enrolled in the consortium, 516 patients underwent testing of the entire panel of 10 different molecular alterations. Two hundred eight patients (54%) tested positive for a specific molecular alteration. Approximately 97% of these molecular alterations were mutually exclusive, with the most common ones being mutations in KRAS (22%) followed by mutations in EGFR-TK (17%) and EML4-ALK fusion gene (7%). More importantly, mutation detection often influenced treatment decisions; for in-

*Division of Oncology, Department of Medicine, Washington University School of Medicine, St. Louis, MO; †Alvin J. Siteman Cancer Center at Washington University School of Medicine, St. Louis, Missouri; and ‡Division of Medical Oncology, Department of Medicine, Yale University School of Medicine and Smilow Cancer Center, New Haven, Connecticut.

Disclosure: Ramaswamy Govindan, MD, has served as a consultant for Bristol Meyer Squibb, Genentech, Lilly, AstraZeneca, and Glaxo-Smith-Kline.

Address for correspondence: Ramaswamy Govindan, MD, Division of Medical Oncology, Washington University School of Medicine, 660 S. Euclid, Box 8056, St Louis, MO 63110. E-mail: rgovinda@dom.wustl.edu

ISSN: 1556-0864/12/0701-0260

stance at one of the sites, 121 patients were enrolled in the LCMC study, 54% tested positive for a mutation, and 30% of these patients received therapy targeted to their specific mutation, with 19 patients receiving erlotinib as initial therapy, and 16 patients being enrolled in one of the eight industry-sponsored trial linked to this consortium. The future of lung cancer management will be focused on selecting targeted therapies based on molecular testing, and LCMC is an important step in that direction.

First-Line Therapy

The paradigm of administering cytotoxic chemotherapy to all eligible patients with advanced non-small cell lung cancer (NSCLC) is slowly changing, with the use of biomarker testing to select patients for molecularly targeted treatment. Prospective randomized trials have established the effectiveness of gefitinib in the frontline treatment of patients who test positive for the EGFR-TK mutation.[1,4] Nevertheless, these trials were primarily conducted in Asian populations. The European Tarceva versus chemotherapy (EURTAC) is a phase III study comparing single-agent erlotinib to platinum doublet in the frontline treatment of patients with NSCLC and had activating EGFR-TK mutations.[5] Treatment with erlotinib was associated with a significant improvement in the primary end point progression-free survival (PFS) in patients receiving erlotinib compared with patients receiving chemotherapy alone; median PFS 9.4 months versus 5.2 months (hazard ratio [HR], 0.42; $p < 0.0001$). Preliminary data regarding overall survival (OS) did not identify a significant difference between the two groups possibly because of crossover to erlotinib in the second-line setting; HR = 0.8 (95% confidence interval [CI], 0.47–1.37; $p = 0.42$). Similar results were reported from the phase III OPTIMAL study, which randomized patients with EGFR-TK mutations to either erlotinib or platinum doublet, with significantly higher PFS in patients receiving erlotinib, compared with the chemotherapy group.[6] (Table 1) Results from these two studies show that frontline treatment with erlotinib is an appropriate choice for previously untreated patients with metastatic NSCLC, whose tumors have activating mutations of the EGFR-TK domain.

Second-Line Chemotherapy

Targeting Met kinase

The C-MET gene is a potential therapeutic target in NSCLC, and it is reported to be overexpressed in >75% of all resected lung adenocarcinoma.[7] Furthermore, activation of the Met TK pathway has been shown to have oncogenic activity.[8] In addition, Met amplification has been associated with development of resistance in patients with EGFR-TK mutation treated with gefitinib.[9]

MetMAb is a monovalent antibody that inhibits the activation of the C-Met TK receptor by its ligand hepatocyte growth factor.[10] In a phase II randomized trial, patients ($n = 137$) with advanced NSCLC were randomized to receive either erlotinib alone or erlotinib with MetMAb in the second- and third-line setting with the primary objectives of determining PFS in the intention-to-treat population and in patients who were positive for tumor Met expression by immunohistochemistry (IHC). Patients on the erlotinib only arm were allowed to crossover to MetMAb on progression. There was no significant improvement in PFS between the two study arms in the intention-to-treat population. However, in patients whose tumor tissue was positive for Met expression by IHC, there was significant improvement in PFS for patients treated with MetMAb and erlotinib than patients receiving erlotinib alone; median PFS 2.9 months versus 1.5 months ($p = 0.042$). Similarly in the Met-positive subgroup, treatment with MetMAb and erlotinib was associated with better OS compared with erlotinib alone; median OS 12.6 versus 3.8 months ($p = 0.002$). The addition of MetMAb did not result in any unexpected toxicities. The findings in this study suggest that Met expression by IHC can help select patients who are likely to benefit from the addition of MetMAb to erlotinib in the second- and third-line treatment of advanced NSCLC. The combination of erlotinib and MetMAb is now being evaluated in an ongoing phase III trial.

ALK Inhibition in Patients with NSCLC

EML4-ALK is a novel fusion gene present in ~5% of patients with NSCLC and is associated with excellent therapeutic response to treatment with an ALK kinase inhibitor.[2,11,12] Shaw et al.[13] demonstrated that patients with EML4-ALK fusion protein had a better outcome with crizotinib, a dual Met and ALK kinase, compared with standard chemotherapy, based on a retrospective study, using three different patient cohorts in the second-line setting—ALK-positive patients treated with crizotinib ($n = 30$), ALK-positive patients who did not receive second-line crizotinib ($n = 23$), and ALK-negative patients ($n = 125$).

Heat shock proteins (Hsp) function as intracellular chaperones for other proteins to ensure normal cellular function and also play a role in cancer by promoting the activities

TABLE 1. Phase III Trials of Frontline EGFR-TK Inhibitors in the Treatment of Advanced NSCLC

References	No. of Patients with EGFR-TK Mutation	EGFR-TKI Studied	Response Rate (%)		Median PFS (Months)		Median OS (Months)	
			Chemotherapy	EGFR-TKI	Chemotherapy	EGFR-TKI	Chemotherapy	EGFR-TKI
EURTAC[5]	174	Erlotinib	11	55	5.2	9.4	—	—
OPTIMAL[6]	165	Erlotinib	36	83	4.6	13.7	—	—
IPASS[1]	261	Gefitinib	47	71	6.3	9.5	21.9	21.6
NEJ 002[4]	200	Gefitinib	31	74	5.4	10.8	23.6	30.5
WJTOG 3405[32]	177	Gefitinib	32	62	6.3	9.2	—	—

EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; NSCLC, non-small cell lung cancer; PFS, progression-free survival; OS, overall survival.

of other oncogenic proteins.[14] In an open label phase II study, 96 patients with relapsed/refractory NSCLC were treated with Hsp90 inhibitor STA-9090.[15] The study included molecular analysis of tumor tissue to detect EGFR, KRAS, and BRAF mutation status; in addition, fluorescent in situ hybridization and polymerase chain reaction testing for EML4-ALK fusion gene were also performed. Of the four responders in this study, all of them tested positive for the EML4-ALK fusion gene by either polymerase chain reaction or fluorescent in situ hybridization. The treatment was overall well tolerated, and the common adverse events were grade ≤2 diarrhea, nausea, and fatigue. These interesting results require further evaluation and independent confirmation. If confirmed, Hsp90 inhibition may present a novel therapeutic option to target the EML4-ALK fusion gene.

Maintenance Therapy

Maintenance therapy after induction with frontline platinum doublet chemotherapy has now become an important tool in the armamentarium of the oncologist treating patients with advanced NSCLC (Table 2). Previous phase III trials have primarily focused on "switch maintenance" therapy, in which a different drug is used for maintenance treatment, after completing platinum doublet induction therapy.[16–19] The PARAMOUNT study is the first phase III randomized trial to explore the benefit of "continuation maintenance," in which the drug used in the maintenance phase is part of the initial induction therapy. In this trial, treatment naive patients with advanced NSCLC, with stable disease or partial response after four cycles of platinum and pemetrexed combination, were randomized to receive either maintenance pemetrexed or placebo, with the primary end point of PFS.[20] Patients receiving pemetrexed maintenance had better (independently assessed) PFS than patients receiving placebo; 3.9 months versus 2.6 months; $p = 0.0002$. Maintenance of pemetrexed was associated with higher incidence of fatigue and cytopenias, but there were no unexpected toxicities.

"Switch maintenance" with erlotinib in unselected patients has been shown to prolong PFS compared with placebo alone after induction with platinum-based chemotherapy.[17–19] The INFORM was a randomized trial in which patients from China ($n = 296$) with advanced NSCLC were randomized to receive gefitinib or placebo if they had stable disease or response after four cycles of platinum doublet chemotherapy.[21] The primary end point was PFS, and gefitinib maintenance was associated with improved PFS compared with placebo; 4.8 months versus 2.6 months; $p < 0.0001$. Tumor tissue was available for EGFR-TK mutations testing in a small number of patients ($n = 79$). Subanalysis identified that patients ($n = 30$) with activating mutations in the EGFR-TK domain had better PFS with gefitinib maintenance than placebo; 16.6 months versus 2.8 months. There was no significant improvement in PFS with gefitinib maintenance for patients with the wild-type EGFR-TK gene. In the phase III SATURN trial, maintenance therapy with erlotinib was associated with improved PFS in patients with EGFR-TK mutations (HR = 0.1; 95% CI, 0.04–0.25; $p < 0.0001$) and patients with wild-type EGFR (HR = 0.78; 95% CI, 0.63–0.96; $p = 0.02$). However, the magnitude of benefit was significantly better in patients with activating EGFR-TK mutations.[22] Results from these two studies suggest that benefit from maintenance therapy with EGFR-TK inhibitors is primarily in patients with activating EGFR mutations.

Preliminary findings from the INFORM and PARAMOUNT studies have shown small but significant improvement in PFS from maintenance therapy with either pemetrexed or an EGFR-TK inhibitor. Subset analysis from the INFORM trial indicates that the benefit from gefitinib maintenance may be confined to patients with EGFR-TK mutations. The PARAMOUNT study shows that continuation maintenance with pemetrexed is effective and safe. Taken together with previous phase III studies (Table 2), it is clear that maintenance therapy improves PFS in patients with NSCLC

TABLE 2. Phase III Trials of Maintenance Therapy

Study	No. of Patients	Induction Therapy	No. of Patients Randomized	Maintenance Therapy	Median PFS (Months)	*p*
Paz-Ares et al.[20]	939	Cisplatin + pemetrexed	539	Pemetrexed	3.9	0.0002
				Placebo	2.6	
Zhang et al.[21]	—	Platinum doublet	296	Gefitinib	4.8	0.0001
				Placebo	2.6	
Ciuleanu T et al.[33]	—	Platinum doublet	663	Pemetrexed	4.3	<0.0001
				Placebo	2.6	
Fidias et al.[16]	566	Carboplatin + Gemcitabine	309	Docetaxel	5.7	0.0001
				Placebo	2.7	
Perol et al.[19]	834	Cisplatin + gemcitabine	309	Gemcitabine	3.8	0.002
				Placebo	1.9	
Perol et al.[19]	834	Cisplatin + gemcitabine	309	Erlotinib	2.9	0.002
				Placebo	1.9	
Cappuzzo et al.[17]	1949	Platinum doublet	889	Erlotinib	2.9	<0.0001
				placebo	2.6	
Kabbinavar et al.[18]	—	Platinum doublet + bevacizumab	768	Erlotinib + bevacizumab	4.8	0.012
				Bevacizumab	3.8	

who benefit from frontline platinum-based therapy. However, improvement in PFS did not result in better quality of life, and most maintenance studies did not show an improvement in OS.[23] There are also issues with the study design of these trials because a third of the patients in the placebo or observation arm did not receive second-line therapy, and there was significant treatment variation in patients who did receive second-line therapy. It is important that these issues are addressed in future maintenance studies in NSCLC.

Resectable NSCLC

Adjuvant Chemotherapy in Patients with Stage IB Disease

The benefit of adjuvant chemotherapy is clear in patients with stage II and III disease, but remains unclear in patients with stage IB disease. The Cancer and Leukemia Group B 9633 study failed to demonstrate a survival advantage for adjuvant chemotherapy in the intention-to-treat population, although an unplanned subset analysis had suggested a statistically significant improvement in survival in patients with tumors ≥4 cm, who were treated with chemotherapy.[24] An updated report of the Cancer and Leukemia Group B 9633 study was presented at this year's ASCO annual meeting.[25] After a 9-year median follow-up, there continues to be a lack of demonstrable survival benefit of adjuvant chemotherapy in these patients, and the questionable survival benefit in patients with tumors ≥4 cm was also lost according to the updated analysis, although a trend toward improved survival in patients treated with chemotherapy continued to be observed (HR, 0.78; $p = 0.087$). Patients were also stratified according to the new tumor (T) stage descriptors. Again, there was a trend toward improved survival in patients with tumors over 5 cm with a statistically significant improvement in survival in patients with tumors over 7 cm in size, who were treated with adjuvant chemotherapy (HR, 0.52; $p = 0.048$). These results should be interpreted with caution, because this study was underpowered to detect its primary end point as a result of poor accrual, and these exploratory subgroup analyses were not preplanned. Of note, the updated survival analysis of the JBR.10 adjuvant chemotherapy trial, which included patients with stage I and II disease, did not demonstrate a significant improvement in survival in patients with stage IB disease, irrespective of tumor size cutoffs.[26] The role of adjuvant chemotherapy in stage IB in general remains unclear, although there may be patient subsets that benefit from it.

Improving Dose Delivery and Tolerability of Adjuvant Chemotherapy

Toxicity of adjuvant cisplatin-based chemotherapy is an issue we often have to contend with, and this often results in incomplete treatment, treatment refusal, treatment delays, and dose reductions. The most widely studied regimen in the adjuvant setting is the combination of cisplatin and vinorelbine. Pemetrexed along with cisplatin has been demonstrated to improve survival in patients with metastatic disease, although this benefit was primarily seen in patients with nonsquamous histology. Extrapolating from the data in the metastatic setting, in practice, cisplatin and pemetrexed is being used in the adjuvant setting and is endorsed by the National Comprehensive Cancer Network as an alternative treatment regimen. This combination was studied in a randomized phase II trial, comparing cisplatin and pemetrexed with cisplatin and vinorelbine in the adjuvant setting, with the primary end point of feasibility, which was defined as no death from cancer, toxicity or comorbidity, no premature withdrawals, and no dose-limiting toxicity.[27] Secondary end points were drug delivery and efficacy. Of the 132 patients randomized, 43% had squamous histology and 38% had stage IB disease. The study met its primary end point with a feasibility rate of 95.5% for cisplatin and pemetrexed (95% CI, 87.5–99.1), compared with a rate of 75.4% (95% CI, 63.1–85.2) for cisplatin and vinorelbine; $p = 0.001$. The lower feasibility rate with cisplatin and vinorelbine was primarily due to a higher rate of dose-limiting toxicity (15.4 compared with 3%) and withdrawal of consent (6.2 versus 0%). Drug delivery was also superior for the cisplatin and pemetrexed arm. For efficacy data, a longer follow-up is needed, although how we would interpret these data is unclear, given the high rate of patients with squamous histology and stage I disease.

Adjuvant Chemotherapy in the Elderly

Subgroup analysis of the JBR.10 and LACE meta-analysis demonstrated a benefit of adjuvant cisplatin-based chemotherapy in elderly patients with NSCLC, with acceptable toxicity. However, the actual utilization of adjuvant chemotherapy in the elderly population (older than 70 years) with NSCLC is not known. Cuffe et al.[28] described the use of chemotherapy in elderly patients with NSCLC, using the population-based Ontario Cancer Registry, and identified 6304 patients between 2001 and 2006, who underwent resection for NSCLC, of which 2746 were elderly (older than 70 years). Use of adjuvant chemotherapy was noted to decline by age, with 43% of patients younger than 70 years, 23% in 70 to 74 years, 13% in 75 to 79 years, and 5% older than 80 years receiving adjuvant platinum-based chemotherapy. Approximately 70% of elderly patients who received adjuvant chemotherapy were treated with cisplatin, compared with 85% of those younger than 70 years. Dose modifications and substitutions were similar in patients younger than 70 years. Although the use of adjuvant chemotherapy was seen to decline by age, in this study adjuvant chemotherapy was associated with a statistically significant survival benefit in elderly patients.

Cisplatin Versus Carboplatin in the Adjuvant Setting

Gu et al.[29] retrospectively compared the outcome of patients with NSCLC who received cisplatin and carboplatin-based chemotherapy using the Surveillance Epidemiology End Results Medicare database. This study included 3324 patients above 65 years, who underwent resection for stage II to IIIA NSCLC between 1992 and 2005. Of these patients, 19% received platinum-based adjuvant chemotherapy within 3 months of surgery, with better survival outcome compared with patients who did not receive adjuvant chemotherapy

(HR, 0.79; 95% CI, 0.71–0.89). Carboplatin was the more commonly used regimen (76.9%) and no survival difference was observed between the groups who received cisplatin or carboplatin. Although these findings are intriguing, there are no prospective studies to support the use of carboplatin-based adjuvant chemotherapy.

Small Cell Lung Cancer

Amrubicin is a third-generation synthetic anthracycline derivative that showed a significant improvement in response rates compared with topotecan (44 versus 15%, $p = 0.02$) in patients with chemotherapy-sensitive SCLC.[30] Although neither the PFS (4.5 versus 3.3 months) nor the OS (9.2 versus 7.6 months) reached statistical significance, the encouraging results from the phase II trial led to the ACT-1, a large randomized phase III trial where 637 patients with either sensitive or refractory disease were randomized in a 2:1 ratio to receive amrubicin 40 mg/m^2 on days 1 to 3 or topotecan 1.5 mg/m^2 from days 1 to 5, with OS as the primary end point.[31] Similar to the results from the phase II study, amrubicin was associated with a significant improvement in response rates (31 versus 17%, $p = 0.0002$) but not in OS (7.5 versus 7.8 months). In the subset of patients with refractory disease, there was a small benefit from amrubicin (6.2 versus 5.7 months, $p = 0.047$). It is difficult to make meaningful progress in the treatment of SCLC, without understanding the biology of this disease, particularly in the case of relapsed SCLC.

CONCLUSION

The presentations from 47th annual meeting of the ASCO address several questions relevant to the clinical management of lung cancer including the role of first-line treatment with erlotinib, maintenance therapy with pemetrexed and gefitinib, and adjuvant chemotherapy in patients with stage I disease. There were also several presentations on emerging targeted therapies, and more importantly the LCMC consortium is an important step toward developing personalized therapy for patients with NSCLC. However, this is only a beginning and further efforts are required to develop effective customized treatments for lung cancer. It is likely that the ongoing large-scale lung cancer sequencing efforts will shed considerable light on novel targets and tumor biology. Future efforts on developing targeted therapies should focus, first and foremost, on identifying appropriate molecular subsets.

REFERENCES

1. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med* 2009;361:947–957.
2. Kwak EL, Bang Y-J, Camidge DR, et al. Anaplastic lymphoma kinase inhibition in non–small-cell lung cancer. *N Engl J Med* 2010;363:1693–1703.
3. Kris MG, Johnson BE, Kwiatkowski DJ, et al. Identification of driver mutations in tumor specimens from 1,000 patients with lung adenocarcinoma: The NCI's Lung Cancer Mutation Consortium (LCMC). *J Clin Oncol* 2011;29(abstract CRA7506).
4. Maemondo M, Inoue A, Kobayashi K, et al. Gefitinib or chemotherapy for non–small-cell lung cancer with mutated EGFR. *N Engl J Med* 2010;362:2380–2388.
5. Rosell R, Gervais R, Vergnenegre A, et al. Erlotinib versus chemotherapy (CT) in advanced non-small cell lung cancer (NSCLC) patients (p) with epidermal growth factor receptor (EGFR) mutations: interim results of the European Erlotinib Versus Chemotherapy (EURTAC) phase III randomized trial. *J Clin Oncol* 2011;29:abstract 7503 (ASCO Meeting Abstracts).
6. Zhou C, Wu YL, Chen G, et al. Updated efficacy and quality-of-life (QoL) analyses in OPTIMAL, a phase III, randomized, open-label study of first-line erlotinib versus gemcitabine/carboplatin in patients with EGFR-activating mutation-positive (EGFR Act Mut+) advanced non-small cell lung cancer (NSCLC). *J Clin Oncol* 2011;29:abstract 7520 (ASCO Meeting Abstracts).
7. Nakamura Y, Niki T, Goto A, et al. c-Met activation in lung adenocarcinoma tissues: an immunohistochemical analysis. *Cancer Sci* 2007;98:1006–1013.
8. Iyer A, Kmiecik TE, Park M, et al. Structure, tissue-specific expression, and transforming activity of the mouse met protooncogene. *Cell Growth Differ* 1990;1:87–95.
9. Engelman JA, Zejnullahu K, Mitsudomi T, et al. MET amplification leads to gefitinib resistance in lung cancer by activating ERBB3 signaling. *Science* 2007;316:1039–1043.
10. Spigel DR, Ervin TJ, Ramlau R, et al. Final efficacy results from OAM4558g, a randomized phase II study evaluating MetMAb or placebo in combination with erlotinib in advanced NSCLC. *J Clin Oncol* 2011;29:abstract 7505 (ASCO Meeting Abstracts).
11. Soda M, Choi YL, Enomoto M, et al. Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer. *Nature* 2007;448:561–566.
12. Shaw AT, Yeap BY, Mino-Kenudson M, et al. Clinical features and outcome of patients with non–small-cell lung cancer who harbor EML4-ALK. *J Clin Oncol* 2009;27:4247–4253.
13. Shaw AT, Yeap BY, Solomon BJ, et al. Impact of crizotinib on survival in patients with advanced, ALK-positive NSCLC compared with historical controls. *J Clin Oncol* 2011;29:abstract 7507 (ASCO Meeting Abstracts).
14. Whitesell L, Mimnaugh EG, De Costa B, et al. Inhibition of heat shock protein HSP90-pp60v-src heteroprotein complex formation by benzoquinone ansamycins: essential role for stress proteins in oncogenic transformation. *Proc Natl Acad Sci U S A* 1994;91:8324–8328.
15. Wong K, Koczywas M, Goldman JW, et al. An open-label phase II study of the Hsp90 inhibitor ganetespib (STA-9090) as monotherapy in patients with advanced non-small cell lung cancer (NSCLC). *J Clin Oncol* 2011;29:abstract 7500 (ASCO Meeting Abstracts).
16. Fidias PM, Dakhil SR, Lyss AP, et al. Phase III study of immediate compared with delayed docetaxel after front-line therapy with gemcitabine plus carboplatin in advanced non-small-cell lung cancer. *J Clin Oncol* 2009;27:591–598.
17. Cappuzzo F, Ciuleanu T, Stelmakh L, et al; SATURN investigators. Erlotinib as maintenance treatment in advanced non-small-cell lung cancer: a multicentre, randomised, placebo-controlled phase 3 study. *Lancet Oncol* 2010;11:521–529.
18. Kabbinavar FF, Miller VA, Johnson BE, et al. Overall survival (OS) in ATLAS, a phase IIIb trial comparing bevacizumab (B) therapy with or without erlotinib (E) after completion of chemotherapy (chemo) with B for first-line treatment of locally advanced, recurrent, or metastatic non-small cell lung cancer (NSCLC). *J Clin Oncol* 2010;28:abstract 7526 (ASCO Meeting Abstracts).
19. Perol M, Chouaid C, Milleron BJ, et al. Maintenance with either gemcitabine or erlotinib versus observation with predefined second-line treatment after cisplatin-gemcitabine induction chemotherapy in advanced NSCLC: IFCT-GFPC 0502 phase III study. *J Clin Oncol* 2010;28:abstract 7507 (ASCO Meeting Abstracts).
20. Paz-Ares LG, De Marinis F, Dediu M, et al. PARAMOUNT: phase III study of maintenance pemetrexed (pem) plus best supportive care (BSC) versus placebo plus BSC immediately following induction treatment with pem plus cisplatin for advanced nonsquamous non-small cell lung cancer (NSCLC). *J Clin Oncol* 2011;29:CRA 7510 (ASCO Meeting Abstracts).
21. Zhang L, Shenglin M, Song X, et al. Efficacy, tolerability, and biomarker analyses from a phase III, randomized, placebo-controlled, parallel group study of gefitinib as maintenance therapy in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC;

INFORM; C-TONG 0804). *J Clin Oncol* 2011;29:LBA 7511 (ASCO Meeting Abstracts).
22. Brugger W, Kim J-H, Hansen O. Molecular markers and clinical outcome with erlotinib: results from the phase III placebo-controlled SATURN study of maintenance therapy for advanced NSCLC. *J Thorac Oncol* 2009;4:S348–S349.
23. Stinchcombe TE, Socinski MA. Maintenance therapy in advanced non-small cell lung cancer: current status and future implications. *J Thorac Oncol* 2011;6:174–182.
24. Strauss GM, Herndon JE, II, Maddaus MA, et al. Adjuvant paclitaxel plus carboplatin compared with observation in stage IB non-small-cell lung cancer: CALGB 9633 with the Cancer and Leukemia Group B, Radiation Therapy Oncology Group, and North Central Cancer Treatment Group Study Groups. *J Clin Oncol* 2008;26:5043–5051.
25. Strauss GM, Wang XF, Maddaus M, et al. Adjuvant chemotherapy (AC) in stage IB non-small cell lung cancer (NSCLC): Long-term follow-up of Cancer and Leukemia Group B (CALGB) 9633. *J Clin Oncol* 2011;29:abstract 7015 (ASCO Meeting Abstracts).
26. Butts CA, Ding K, Seymour L, et al. Randomized phase III trial of vinorelbine plus cisplatin compared with observation in completely resected stage IB and II non-small-cell lung cancer: updated survival analysis of JBR-10. *J Clin Oncol* 2010;28:29–34.
27. Kreuter M, Vansteenkiste JF, Fischer JR, et al. Randomized phase II trial on refinement of early-stage NSCLC adjuvant chemotherapy with cisplatin and pemetrexed (CPx) versus cisplatin and vinorelbine (CVb): TREAT. *J Clin Oncol* 2011;29:abstract 7002 (ASCO Meeting Abstracts).
28. Cuffe S, Booth CM, Peng Y, et al. Adoption of adjuvant chemotherapy (ACT) for non-small cell lung cancer (NSCLC) in the elderly: a population-based outcomes study. *J Clin Oncol* 2011;29:abstract 7012 (ASCO Meeting Abstracts).
29. Gu F, Strauss GM, Wisnivesky JP. Platinum-based adjuvant chemotherapy (ACT) in elderly patients with non-small cell lung cancer (NSCLC) in the SEER-Medicare database: comparison between carboplatin- and cisplatin-based regimens. *J Clin Oncol* 2011;29:abstract 7014 (ASCO Meeting Abstracts).
30. Jotte R, Conkling P, Reynolds C, et al. Randomized phase II trial of single-agent amrubicin or topotecan as second-line treatment in patients with small-cell lung cancer sensitive to first-line platinum-based chemotherapy. *J Clin Oncol* 2011;29:287–293.
31. Jotte R, Von Pawel J, Spigel DR, et al. Randomized phase III trial of amrubicin versus topotecan (Topo) as second-line treatment for small cell lung cancer (SCLC). *J Clin Oncol* 2011;29:abstract 7000 (ASCO Meeting Abstracts).
32. Mitsudomi T, Morita S, Yatabe Y, et al. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. *The Lancet Oncol* 2010;11:121–128.
33. Ciuleanu T, Brodowicz T, Zielinski C, et al. Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care for non-small-cell lung cancer: a randomised, double-blind, phase 3 study. *Lancet* 2009;374:1432–1440.

